Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *84* (2) 119–128 (2019)
JSCS–5170
UDC 547.77/.81+542.913:615.279'28
Original scientific paper

Multicomponent synthesis of new bis(pyranopyrazoles) and their antimicrobial–antioxidant evaluations

MOHAMAD YUSUF* and SALONI THAKUR

Department of Chemistry, Punjabi University, Patiala-147002, Punjab, India

(Received 7 November 2017, revised 13 August, accepted 18 September 2018)

Abstract: One-pot, three-component reactions were utilized to obtain a series of new symmetrical bis(pyranopyrazoles) built around six rigid linkers in good yields and in the short durations under normal conditions. The structures of the prepared compounds were confirmed using their IR, ^{1}H-NMR, ^{13}C-NMR and ESI-MS spectral parameters. The bis(pyranopyrazoles) **3b** and **3f** exhibited significant antimicrobial action against *Klebsiella pneumoniae*, *Fusarium oxysporum* and *Penicillium glabrum* at a minimum inhibitory concentration (*MIC*) value of 3.12 μg mL^{-1}, which is equivalent to the *MIC* of the standard drug. *trans*-Butene-linked bis(pyranopyrazole) **3f** was also associated with a good radical scavenging activity similar to that of ascorbic acid (a standard antioxidant).

Keywords: pyrazole; dibenzaldehydes; rigid chain linkers; atom economy; antimicrobial activity; antioxidant property.

INTRODUCTION

Organic chemists are continuously working on the development of simple and ecofriendly protocols to obtain useful heterocyclic products.[1,2] Multicomponent reactions are regarded as reliable tools for the synthesis of simple and exotic molecules in a single step. These reactions are also beneficial because of their synthetic convergency, higher selectivity and atom-economy.[3] Pyran and its derivatives have been associated with a broad range of medicinal properties.[4–9] Pyrazole rings act as the core nucleus in many drugs, such as anti-tumor, antipyretic, antidiabetic, anti-inflammatory, antidepressant and antihypertensive agents.[10–15] In pyranopyrazoles, two heterocyclic moieties, pyran and pyrazole, are present together in a single molecular framework.[16] These heterocycles are found to be associated with numerous biological properties, such as analgesic,[17] vasodilator,[18] anticancer,[19,20] antifungal,[21] inhibitory on human Chk1 kinase[22] and molluscicidal,[23] and are also found to act as biodegradable agrochemicals.[24] It is clear from a literature study that enough progress has been made over the

* Corresponding author. E-mail: yusuf_sah04@yahoo.co.in
https://doi.org/10.2298/JSC171107074Y

past decades in the synthesis of pyranopyrazoles using various methodologies, such as cinchona alkaloid being used as catalyst,[25] per-6-amino-*β*-cyclodextrin acting as a supramolecular host and the base catalyst in solvent-free synthesis of substituted dihydropyrano[2,3-*c*]pyrazole derivatives.[26] Babaie and Sheibani synthesized pyranopyrazoles using nano-sized MgO as a heterogeneous catalyst in the presence of different solvents (water, ethanol and acetonitrile).[27] Tayade *et al*. performed an effective one-pot synthesis of pyranopyrazoles at room temperature in the presence of water using 1-methyl-1*H*-imidazole as the base.[28] The grinding technique[29] and the highly efficient choline chloride/urea deep eutectic solvent[30] have also been used for the synthesis of pyranopyrazole. Similarly, glycine-catalysed,[31] DABCO-catalysed,[32] ionic liquid-catalysed,[33] iron-doped calcium oxalate heterogeneous catalysed[34] and L-tyrosine catalysed[35] reactions have been used for the synthesis of dihydropyrano[2,3-*c*]pyrazole. These heterocycles are also realized prominently in aqueous medium using a variety of bases (morpholine, piperazine, piperidine, pyrrolidine, K_2CO_3 and Et_3N).[16] The linking of two pyranopyrazoles together through carbon chains leads to the generation of bispyranopyrazoles. With the best of our efforts, only three papers incorporating the study of bispyranopyrazoles could be found.[36–38] In continuation of an ongoing study on bisheterocycles,[39–44] the present research work was focused on the synthesis of new rigid chain linked bis(pyranopyrazoles) **3a**–**f** using three component condensation reactions of malononitrile, pyrazolone and dibenzaldehydes. The major impetus behind these investigations was to study the antimicrobial and antioxidant properties of the newly prepared symmetrical bisheterocycles.

EXPERIMENTAL

General

The melting points of the synthesized products were taken in open-end capillaries and are uncorrected. The purity of the prepared compounds was checked by silica gel thin layer chromatography using iodine vapor visualization. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 MHz NMR spectrometer with tetramethylsilane (TMS) as the internal standard. The chemical shifts are reported as delta (ppm) values. A Perkin–Elmer RXIFT-IR spectrometer and a Waters Micromass Q-Tof micro Mass spectrometer were used for obtaining the IR and mass spectra, respectively. Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

The dibezaldehydes **2a–f** were prepared using a literature method.[45]

*Syntheses of dibezaldehydes **2a–f***

*4,4'-[[[1,1'-Biphenyl]4,4'-diyl]bis(methyleneoxy)]bisbenzaldehyde (**2a**)*. A mixture of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol), 4, 4′-bis(chloromethyl)diphenyl (1.25 g, 0.005 mol), KOH (0.5 g, 0.008 mol) and water (20.0 mL) was reacted on a magnetic stirrer at 45 °C for 3 h. All the components dissolved completely on heating. The formation of the product was checked on thin layer chromatographic plates (hexane:ethylacetate (2:1) eluent). The successful completion of the reaction provided a brown solid that was further recrystallized from methanol to yield pure compound **2a** (yield: 85 %; m.p.: 225–227 °C).

*4,4′-[But-2-yne-1,4-diylbis(oxy)]bisbenzaldehyde (**2b**)*. The dibenzaldehyde **2b** was synthesized in the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with 1,4-dichloro-2--butyne (0.64 g, 0.005 mol) under similar conditions to those described above for **2a**. Yield: 61 %; m.p.: 140–142 °C.

*4,4′-[1,2-Phenylenebis(methyleneoxy)]bisbenzaldehyde (**2c**)*. The reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with *α*,*α′*-dibromo-*o*-xylene (1.32 g, 0.005 mol) under similar conditions to those described above for **2a** resulted in the formation of dibenzaldehyde **2c**. Yield: 81 %; m.p.: 146–148 °C.

*4,4′-[1,4-Phenylenebis(methyleneoxy)]bisbenzaldehyde (**2d**)*. The dibenzaldehyde **2d** was obtained in the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with *α*,*α′*-dibromo--*p*-xylene (1.32 g, 0.005 mol) under similar conditions to those described above for **2a**. Yield: 58 %; m.p.:152–154 °C.

*4,4′-[1,3-Phenylenebis(methyleneoxy)]bisbenzaldehyde (**2e**)*. The dibenzaldehyde **2e** was synthesized in the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with *α*,*α′*-dibromo-*m*-xylene (1.32 g, 0.005 mol) under similar conditions to those described above for **2a**. Yield: 62 %; m.p.: 100–102 °C.

trans-*4,4′-[But-2-ene-1,4-diylbis(oxy)]dibenzaldehyde (**2f**)*. The dibenzaldehyde **2f** was prepared from the reaction of 4-hydroxybenzaldehyde (1.22 g, 0.01 mol) with *trans*-1,4-dibromo-2-butene (1.06 g, 0.005 mol) under the similar conditions as described above for **2a**. Yield: 79 %; m.p.: 126–128 °C.

The physical and spectral data of dibenzaldehydes **2a**–**f** were found to be similar to those reported in the literature.[45]

*Synthesis of bis(pyranopyrazoles) **3a**–**f***

*4,4′-[[1,1′-Biphenyl]-4,4′-diylbis(methyleneoxy-4,1-phenylene)]bis(6-amino-3-methyl--1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (**3a**)*. A mixture of dibenzaldehyde **2a** (0.84 g, 0.002 mol), malononitrile (0.26 g, 0.004 mol), 2,4-dihydro-5-methyl-3*H*-pyrazol-3--one (0.392 g, 0.004 mol) and ethanol (25.0 mL) was stirred at 50 °C for 2 h.[37] Thin layer chromatography was thoroughly used for checking the progress of the reaction. The resulting reaction mixture was cooled in an ice bath to provide a solid substance that was further crystallized from ethanol to yield pure compound **3a**.

*4,4′-[But-2-yne-1,4-diylbis(oxy-4,1-phenylene)]bis(6-amino-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (**3b**)*. Compound **3b** was prepared by reacting dibenzaldehyde **2b** (0.59 g, 0.002 mol), malononitrile (0.26 g, 0.004 mol) and 2,4-dihydro-5-methyl--3*H*-pyrazol-3-one (0.392 g, 0.004 mol) under similar conditions to those used for **3a**.

*4,4′-[1,2-Phenylenebis(methyleneoxy-4,1-phenylene)]bis(6-amino-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (**3c**)*. Compound **3c** was synthesized in the reaction of dibenzaldehyde **2c** (0.69 g, 0.002 mol) with malononitrile (0.26 g, 0.004 mol) and 2,4--dihydro-5-methyl-3*H*-pyrazol-3-one (0.392 g, 0.004 mol) under similar conditions to those discussed for **3a**.

*4,4′-[1,4-Phenylenebis(methyleneoxy-4,1-phenylene)]bis(6-amino-3-methyl--1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (**3d**)*. Compound **3d** was obtained by reacting a mixture of dibenzaldehyde **2d** (0.69 g, 0.002 mol), malononitrile (0.26 g, 0.004 mol) and 2,4-dihydro-5-methyl-3*H*-pyrazol-3-one (0.392 g, 0.004 mol) under similar conditions to those discussed for **3a**.

*4,4′-[1,3-Phenylenebis(methyleneoxy-4,1-phenylene)]bis(6-amino-3-methyl--1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (**3e**)*. Compound **3e** was prepared in the reaction of a mixture of dibenzaldehyde **2e** (0.69 g, 0.002 mol), malononitrile (0.26 g, 0.004

mol) and 2,4-dihydro-5-methyl-3*H*-pyrazol-3-one (0.392 g, 0.004 mol) under similar conditions to those discussed earlier for **3a**.

trans-*4,4'-[But-2-ene-1,4-diylbis(oxy-4,1-phenylene)]bis(6-amino-3-methyl-1,4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitrile) (**3f**)*. Compound **3f** was prepared in the treatment of dibenzaldehyde **2f** (0.60 g, 0.002 mol) with malononitrile (0.26 g, 0.004 mol) and 2,4-dihydro-5-methyl-3*H*-pyrazol-5-one (0.392 g, 0.004 mol) under similar conditions as discussed for **3a**.

*Antimicrobial evaluation of bis(pyranopyrazoles) **3a**–**f***

The antimicrobial properties of bis(pyranopyrazoles) **3a**–**f** were tested against five bacterial strains, namely *Klebsellia pneumonia* (MTCC 3384), *Pseudomonas* aeruginosa (MTCC 424), *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441), and five fungal strains, *i.e.*, *Aspergillus janus* (MTCC 2751), *Pencillium glabrum* (MTCC 4951), *Fusarium oxysporum* (MTCC 2480), *Aspergillus sclerotiorum* (MTCC 1008) and *Aspergillus niger* (MTCC 281). The serial dilution technique was used to determine the minimum inhibitory concentrations of the newly prepared bis(pyranopyrazoles) **3a–f**, which were evaluated using amoxicillin and fluconazole as standard drugs and DMSO as the negative control.[46] The minimum inhibitory concentration (*MIC* / μg mL^{-1}) of the bis(pyranopyrazoles) were determined using different dilutions of the corresponding products. The susceptibility of the bacterial and fungal strains to test compounds was determined by the appearance of turbidity. The minimum concentration that was required to prevent the growth of the bacteria and fungi was regarded as *MIC*. All the bacteria strains were grown at 37 °C for 24 h and the fungi strains at 28 °C for 72 h.

DPPH radical scavenging activity

2,2-Diphenyl-1-picrylhydrazyl (DPPH) exists as a stable free radical and thus is used to investigate radical scavenging activity. In this scavenging technique, bis(pyranopyrazoles) **3a**–**f** are reacted with DPPH (deep violet color) and converted it to a yellow colored *α*,*α*-diphenyl-*β*-picrylhydrazine. The degree with which the discoloration occurred stipulate the radical-scavenging potential of the newly synthesized compounds.

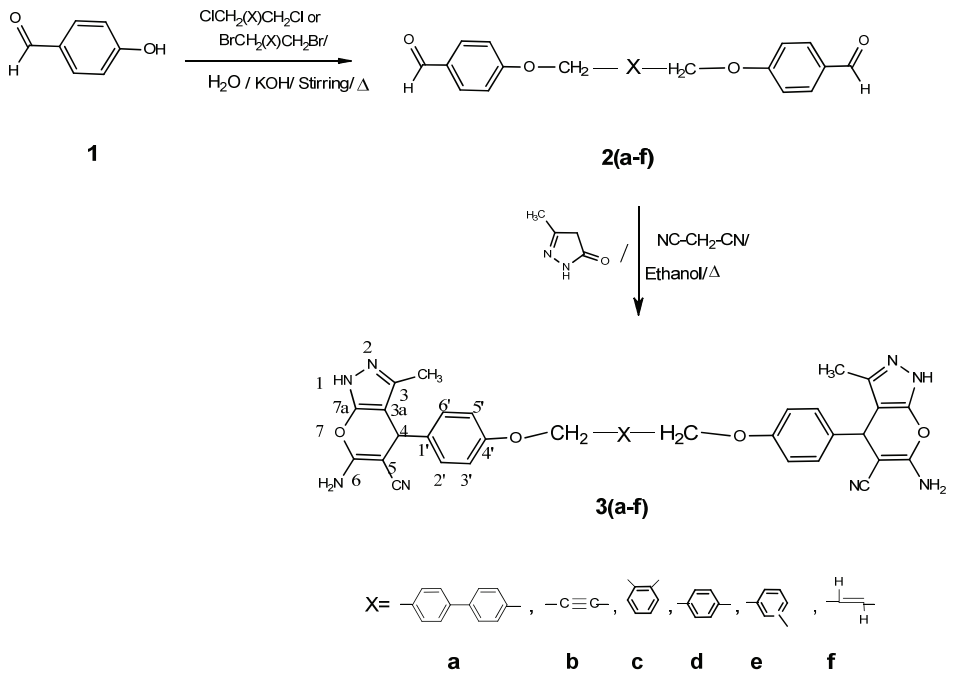
The scavenging activity of **3a**–**f** and ascorbic acid was observed in the concentration range from 50–100 μg mL^{-1}. After mixing a solution of DPPH (0.004 %) and test solutions of different concentrations, both in methanol, these were left for an incubation period of 30 min at room temperature and then the absorbance was measured in a UV spectrophotometer at 517 nm.

RESULTS AND DISCUSSION

The bis(pyranopyrazoles) **3a**–**f** required for the present study were synthesized in three component reactions of dibenzaldehydes, malononitrile and pyrazole under stirring in an alcoholic medium, Scheme 1. The dibenzaldehydes **2a**–**f**[45] needed for these reactions were prepared in good yields in the reaction of *p*-hydroxybenzaldehyde with suitable dihalogenated reagents (*trans*-1,4-dibromo-2-butene, 1,4-dichloro-2-butyne, *α*,*α'*-dibromo-*o*-xylene, *α*,*α'*-dibromo-*m*-xylene, *α*,*α'*-dibromo-*p*-xylene and 4,4′-bis(chloromethyl)diphenyl) in the presence of KOH and H_2O as the medium. The structures of the newly prepared bis-heterocycles **3a**–**f** were fully characterized based on their satisfactory IR, ^{1}H-NMR, ^{13}C-NMR and ESI-MS spectral parameters. The characterization data are given in the Supplementary material.

The IR spectra of **3a**–**f** were very helpful in ascertaining their structures. Thus, they did not exhibit any absorption at 1699–1670 cm^{-1}, indicating the involvement of the carbonyl groups of **2a**–**f** in the formation of the products. The characteristic absorptions due to N–H, C≡N and C=N stretching frequencies were observed at 3471–3150, 2259–2159 and 1638–1592 cm^{-1}, respectively.

In the ^{1}H-NMR (400 MHz, DMSO-d_6) spectra, the aldehydic protons present at δ 10.52–9.86 ppm in the spectra of **2a**–**f** were absent in the spectra of **3a**–**f**, which confirms the involvement of these hydrogens in the formation of the heterocyclic ring. The broad singlets present at δ 12.00–11.74 ppm could be assigned to the 1-NH protons of the pyrazole ring. A noticeable resonance in these spectra was the signal of the H-4 protons of the pyran ring, which appeared as two sharp hydrogen singlets at δ 4.57–4.50 ppm. The *p*-disubstituted benzene ring protons H-2′, 6′ and H-3′, 5′ appeared in the form of two doublets at δ 7.10–6.89 ppm (J_o = 6.8–10.0 Hz) and 6.91–6.57 (J_o = 7.5–10.0 Hz), respectively. The intermediate alkene, alkyne and aromatic linkers produced appropriate signals in the aromatic region (see the Supplementary material). The C_6-NH_2 group protons were found to resonate as four broad proton singlets at δ 6.75–6.04 ppm. In the aliphatic region, the four proton singlets present at δ 5.35–4.72 could be assigned to OCH_2 group. The six protons belonging to two CH_3 groups of the pyrazole ring produced singlets at δ 1.81–1.78 ppm.



Scheme 1. Synthesis of bis(pyranopyrazoles) **3a**–**f**.

The carbon framework of compounds **3a**–**f** was confirmed based on their ^{13}C-NMR (100 MHz, DMSO-d_6) spectra. The carbon atom C-6 resonated at δ 160.85–160.49 ppm due to its direct bonding to the electronegative nitrogen and oxygen atoms. The signals present at δ 156.98–154.70 ppm and 118.30–113.21 ppm could easily be assigned to C-3 and C≡N, respectively. The carbon atoms C-2′, 6′ and C-3′, 5′ appeared at δ 128.40–121.47 ppm and 120.41–110.51 ppm, respectively. The carbon atoms C-7a and C-3a associated to the pyran ring were found at δ 136.37–128.35 and 97.68–97.21 ppm, respectively. The pyran ring carbon atom C-4 was responsible for the generation of suitable signals at δ 36.39–35.50 ppm. The remaining aromatic and internal chain carbon atoms were found at appropriate positions in the aromatic region (see the Supplementary material). Two signals were also located in the region of δ 69.14–57.50 ppm and 9.74–9.69 ppm, which may be assigned to OCH_2 and CH_3 group carbon atoms, respectively.

Antimicrobial evaluation

All the synthesized compounds **3a**–**f** were found to display noticeable antimicrobial behavior against the tested microorganisms. The *MIC* values of bis(pyranopyrazoles) towards the tested bacteria and fungi are given in Table I. Compound **3f** showed the most significant activity against bacterial strains, namely *E. coli*, *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, and two fungal strains, namely *P. glabrum* and *F. oxysporum.* Compound **3b** had noticeable behavior against the bacterial strains *K. pneumoniae* and *S. aureus*, and the fungal strains

TABLE I. MIC data (μg mL^{-1}) for bis(pyranopyazoles) **3a**–**f** against the studied bacteria and fungi

Compound	Gram-negative bacteria			Gram-positive bacteria	
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*S. aureus*	*B. subtilis*
3a	25	50	25	25	50
3b	12.5	**3.12**	12.5	**6.25**	25
3c	12.5	12.5	**6.25**	12.5	25
3d	25	25	25	50	50
3e	12.5	12.5	12.5	25	25
3f	**6.25**	**3.12**	**3.12**	**6.25**	12.5
Amoxicillin	**3.12**	**3.12**	**3.12**	**3.12**	**3.12**
	Fungi				
	A. janus	*P. glabrum*	*A. niger*	*F. oxysporum*	*A. sclerotiorum*
3a	50	25	25	12.5	12.5
3b	25	**3.12**	25	**6.25**	50
3c	12.25	25	25	12.5	50
3d	25	12.5	25	25	12.5
3e	**6.25**	25	12.5	12.5	12.5
3f	12.5	**6.25**	12.5	**3.12**	25
Fluconazole	**3.12**	**3.12**	**3.12**	**3.12**	**3.12**

P. glabrum and *F. oxysporum*. Compound **3a** showed good fungicidal actions against *F. oxysporum* and *A. sclerotiorum* with an *MIC* value of 12.5 μg mL^{-1} and **3d** exhibited similar behavior against *P. glabrum* and *A. sclerotiorum*. Bisheterocyclic **3c** provided important results against the bacterial strain *P. aeruginosa* with an *MIC* of 6.25 μg mL^{-1}, while compound **3e** exhibited an *MIC* of 6.25 μg mL^{-1} against *A. janus*. The 2-butyne **3b** and *trans*-butene **3f** bisheterocycles exhibited the most significant results (*MIC* of 3.12 μg mL^{-1}), which is equivalent to the standard drugs amoxicillin and fluconazole.

Antioxidant activity

DPPH exists as a stable free radical and thus is used to investigate radical scavenging activity. In the DPPH scavenging technique, the degree of discoloration stipulates the radical-scavenging potential of the newly synthesized compounds in comparison to the degree of discoloration caused by ascorbic acid.[47,48] The absorbances at different concentrations of **3a**–**f** and ascorbic acid in the range from 50–100 μg mL^{-1} are given in Table II.

TABLE II. Absorbance at different concentration of bis(pyranopyazoles) **3a**–**f** and ascorbic acid

Compound	Concentration, μg mL^{-1}		
	50	75	100
3a	0.381	0.297	0.191
3b	0.298	0.218	0.168
3c	0.314	0.225	0.171
3d	0.332	0.261	0.196
3e	0.321	0.243	0.182
3f	0.281	0.201	0.162
Control	0.267	0.189	0.143

The percent of inhibition, *I*, of free radical production from DPPH was calculated based on the following equation.[49]

$$I = 100(A_{\text{control}} - A_{\text{sample}}) / A_{\text{control}}$$

where A_{control} represents the absorbance of the control (in a methanolic solution of DPPH) and A_{sample} represents the absorbance of the tested compound (in a methanolic solution of DPPH). The calculated inhibition levels are given in Table III, from which it could be seen that compounds **3b** and **3f** showed very good scavenging capacities while the other compounds **3a**, **3c**, **3d** and **3e** also revealed good results.

CONCLUSIONS

In the present investigations, a quite simple, general and efficient protocol for the synthesis of new bis(pyranopyrazole) **3a–f** built around six types of rigid linkers was developed. The bis(pyranopyrazole) were tested for their antioxidant

TABLE III. Inhibition level (%) at different concentration of **3a**–**f**

Compound	Concentration of bis(pyranopyazole), mg mL^{-1}		
	50	75	100
3a	34.1	48.7	67.0
3b	48.5	62.3	68.7
3c	45.7	61.1	70.4
3d	42.6	54.9	66.8
3e	44.5	58.0	68.5
3f	51.4	65.2	72.0
Ascorbic acid	53.8	67.3	75.6

action and on comparison with ascorbic acid, it could be concluded that **3b** and **3f** exhibited significant radical scavenging activity against DPPH. Compound **3f** showed potent behavior against four bacterial strains, *E. coli*, *P. aeruginosa*, *S. aureus* and *K. pneumoniae*, and two fungal strains, *P. glabrum* and *F. oxysporum.* Bisheterocycle **3b** had remarkable action against the bacterial strains *K. pneumoniae* and *S. aureus*, and fungal strains *P. glabrum* and *F. oxysporum*. The 2-butyne **3b** and *trans*-butene **3f** bis(pyranopyrazoles) were associated with significant antimicrobial results with *MIC* values of 3.12 μg mL^{-1}, which are equivalent to those of the standard drugs amoxicillin and fluconazole.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically on the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. The authors are highly thankful to DST, New Delhi, for providing the financial support for this research work.

ИЗВОД

ВИШЕКОМПОНЕНТНА СИНТЕЗА НОВИХ БИС(ПИРАНПИРАЗОЛА) И ИСПИТИВАЊЕ ЊИХОВЕ АНТИМИКРОБНЕ И АНТИОКСИДАТИВНЕ АКТИВНОСТИ

MOHAMAD YUSUF и SALONI THAKUR

Department of Chemistry, Punjabi University, Patiala-147002, Punjab, India

У трокомпонентној реакцији, у једном реакционом кораку, синтетисана је серија нових симетричних бис(пиранпиразола), у добром приносу и кратком реакционом времену. Структуре производа изграђене су око шест крутих линкера, и окарактерисане су помоћу ИЦ, ^{1}H-NMR, ^{13}C-NMR и ESI-MS спектара. Бис(пиранпиразоли) **3b** и **3f** имају запажену антимикробну активност према микроорганизмима *Klebsiella pneumoniae*, *Fusarium oxysporum* и *Penicillium glabrum* са *MIC* вредношћу од 3,12 μg/ml, једнакој активности лекова коришћених као стандард. Бис-пиранпиразол са *trans*-бутенским линкером **3f** такође показује и добру активност као хватач слободних радикала, блиску активности аскорбинске киселине (антиоксиданс коришћен као стандард).

(Примљено 7. новембра 2017, ревидирано 13. августа, прихваћено 18. септембра 2018)

REFERENCES

1. M. Koohshari, M. Dabiri, P. Salehi, *RSC Adv.* **4** (2014) 10669
2. L. A. Wessjohann, B. Voigt, D. G. Rivera, *Angew. Chem. Int. Ed.* **44** (2005) 4785
3. (a) N. M. Evdokimov, A. S. Kireev, A. A. Yakovenko, M. Y. Antipin, A. Kornienko, *J. Org. Chem.* **72** (2007) 3443; (b) H. Bienayme, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J*. **6** (2000) 3321
4. A. H. Bedair, N. A. El-Hady, M. S. Abd El-Latif, A. H. Fakery, A. M. El-Agrody, *Farmaco* **55** (2000) 708
5. M. J. Perez-Perez, J. Balzarini, J. Rozenski, E. De Clercq, P. Herdewijn, *Bioorg. Med. Chem. Lett.* **5** (1995) 1115
6. A. H. Shamroukh, M. E. A. Zaki, E. M. H. Morsy, F. M. Abdel-Motti, F. M. E. Abdel--Megeid *Arch Pharm. (Weinheim, Ger.)* **340** (2007) 345
7. M. D. Aytemir, U. Calis, M. Ozalp, *Arch. Pharm. (Weinheim, Ger.)* **337** (2004) 281
8. E. Melliou, P. Magiatis, S. Mitaku, A. L. Skaltsounis, A. Pierre, G. Atassi, P. Renard, *Bioorg. Med. Chem*. **9** (2001) 607
9. F. Chabchoub, M. Messaad, L. Chekir-Ghedira, M. Salem, *Eur. J. Med. Chem.* **42** (2007) 715
10. Z.N. Siddiqui, M. Asad, *Indian J. Chem., B* **48** (2009) 1609
11. X. L. Ren, H. B. Li, C. Wu, H. Z. Yang, *Arkivoc* **2005** (xv) (2005) 59
12. C. Almansa, J. Alfon, A.F. de-Arriba, F.L. Cavalcanti, I. Escamilla, L.A. Gomez, A. Miralles, R. Soliva, J. Bartrolí, E. Carceller, M. Merlos, J. García-Rafanell, *J. Med. Chem.* **40** (1997) 547t'
13. H. J. Park, K. Lee, S. J. Park, B. Ahn, J. C. Lee, H. Y. Cho, K. I. Lee, *Bioorg. Med. Chem. Lett.* **15** (2005) 3307
14. P. Cali, L. Naerum, S. Mukhija, A. Hjelmencrantz, *Bioorg. Med. Chem. Lett.* **14** (2004) 5997
15. Y. R. Prasad, A. L. Rao, L. Prasoona, K. Murali, P. P. Kumar, *Bioorg. Med. Chem. Lett.* **15** (2005) 5030
16. G. Vasuki, K. Kumaravel, *Tetrahedron Lett.* **49** (2008) 5636
17. S. C. Kuo, L. J. Huang, H. Nakamura, *J. Med. Chem*. **27** (1984) 539
18. V. K. Ahluwalia, A. Dahiya, V. Garg, *Indian J. Chem., B* **36** (1997) 88
19. J. L. Wang, D. Liu, Z. J. Zheng, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri, Z. Huang, *Proc. Natl. Acad. Sci. U.S.A.* **97** (2009) 7124
20. M. E. A. Zaki, E. M. Morsy, F. M. Abdel-Motti, F. M. E. Abdel-Megei, *Heterocycl. Commun*. **10** (2004) 97
21. M. M. M. Ramiz, I. S. Abdel Hafiz, M. A. M. Abdel Reheim, H. M. Gaber, *J. Chin. Chem. Soc*. **59** (2012) 72
22. N. Foloppe, L. M. Fisher, R. Howes, A. Potter, A. G. S. Robertson, A. E. Surgenor, *Bioorg. Med. Chem*. **14** (2006) 4792
23. a) F. M. Abdelrazek, P. Metz1, O. Kataeva1, A. Jager, S. F. El-Mahrouky, *Arch. Pharm. (Weinheim, Ger.)* **340** (2007) 543; b) F. M. Abdelrazek, F. A. Michael, A. E. Mohamed, *Arch. Pharm. (Weinheim, Ger.)* **339** (2006) 305
24. H. Wamhoff, E. Kroth, K. Strauch, *Synthesis* **11** (1993) 1129
25. S. Gogoi, C.-G. Zhao, *Tetrahedron Lett.* **50** (2009) 2252
26. K. Kanagaraj, K. Pitchumani, *Tetrahedron Lett.* **51** (2010) 3312
27. M. Babaie, H. Sheibani, *Arab. J. Chem.* **4** (2011) 159
28. A. Siddekha, A. Nizama, M.A. Pasha, *Spectrochim. Acta, A* **81** (2011) 431
29. S. Ambethkar, V. Padmini, N. Bhuvanesh, *J. Adv. Res.* **6** (2015) 975

30. A. Moshtaghi Zonouz, D. Moghani, *Synth. Commun.* **46** (2016) 220
31. M. B. Madhusudana Reddy, V. P. Jayashankara, *Synth. Commun*. **40** (2010) 2930
32. A. S. Waghmare, S. S. Pandit, *J. Saudi Chem. Soc*. **21** (2017) 286
33. S. M. Deshmukh, D. P. Hiwarale, *Pharma Chem.* **9** (2017) 109
34. K. K. Gangu, S. Maddila, S. Narayana, S. B. Jonnalagadda *RSC Adv.* **7** (2017) 423
35. A. D. Rupnar, V. P. Pagore, S. U. Tekale, S. U. Shisodia, R. P. Pawar, *Chem. Sinica* **8** (2017) 229
36. M. Mamaghani, R. H. Nia, F. Shirini, K. Tabatabaeian, M. Rassa, *Med. Chem. Res*. **24** (2015) 1916
37. M. Yusuf, M. Kaur, H. S. Sohal, *J. Heterocycl. Chem*. **54** (2017) 706.
38. R. S. Aliabadi, N. O. Mahmoodi, *RSC Adv.* **6** (2016) 85877
39. M. Yusuf, P. Jain, *Arab. J. Chem.* **5** (2012) 93
40. M. Yusuf, P. Jain, *J. Chem. Sci.* **125** (2013) 117
41. M. Yusuf, P. Jain, *J. Heterocycl. Chem*. **51** (2014) 1162
42. M. Yusuf, V. Samdhian, P. Jain, *J. Heterocycl. Chem*. **52** (2015) 692
43. M. Yusuf, I. Solanki, *J. Saudi Chem. Soc*. **21** (2017) 251
44. M. Yusuf, A. Kaur, M. Abid, *J. Heterocycl. Chem*. **54** (2017) 2536
45. M. Yusuf, I. Solanki, P. Jain, *J. Chem. Sci.* **124** (2012) 703
46. K. S. Pandey, N. Khan, *Arch. Pharm. (Weinheim, Ger.)* **341** (2008) 418
47. M. Alothman, R. Bhat, A. A. Karim, *Food Chem.* **115** (2009) 785
48. D. Babu, P. Gurumurthy, S. K. Borra, K. M. Cherian, *J. Med. Plant Res*. **7** (2013) 2898
49. H. Ohkawa, N. Ohisini, K. Yagi, *Anal. Biochem*. **95** (1979) 353.